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D-65926 Frankfurt am Main
ALLEMAGNE

Date of mailing (day/month/year)
21 January 2000 (21.01.00)

Applicant's or agent's file reference
1998/L020 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP99/02715

International filing date (day/month/year)
22 April 1999 (22.04.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

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2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

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Teleprinter No.: 4 1234 700 ho d

3. Further observations, if necessary:
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4. A copy of this notification has been sent to:

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Authorized officer
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Date of mailing (day/month/year) 07 December 1999 (07.12.99)	
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International filing date (day/month/year) 22 April 1999 (22.04.99)	**Priority date** (day/month/year) 23 April 1998 (23.04.98)
Applicant MUKHOPADHYAY, Triptikumar et al	

1. The designated Office is hereby notified of its election made:

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16 November 1999 (16.11.99)

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(54) Title: A PROCESS FOR THE CONVERSION OF ECHINOCANDIN CLASS OF PEPTIDES TO THEIR C4–HOMOTYROSINE MONODEOXY ANALOGUES

(57) Abstract

The invention relates to a process for the conversion of echinocandin class of peptides to their C4–homotyrosine monodeoxy analogues, particularly mulundocandin to deoxy–mulundocandin, which consists of a single step selective reduction of C4–htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues under neutral conditions without prior protection/deprotection of the equally facile C5–Om (ornithine) hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture.

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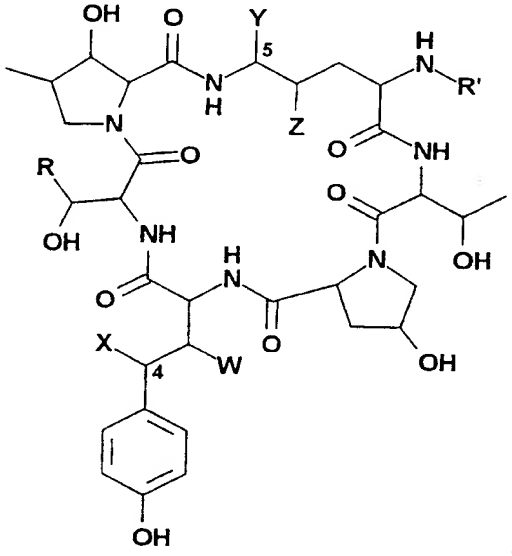
A process for the conversion of echinocandin class of peptides to their C4-homotyrosine monodeoxy analogues

This invention relates to a process for the conversion of echinocandin class of peptides of the formula I



(I)

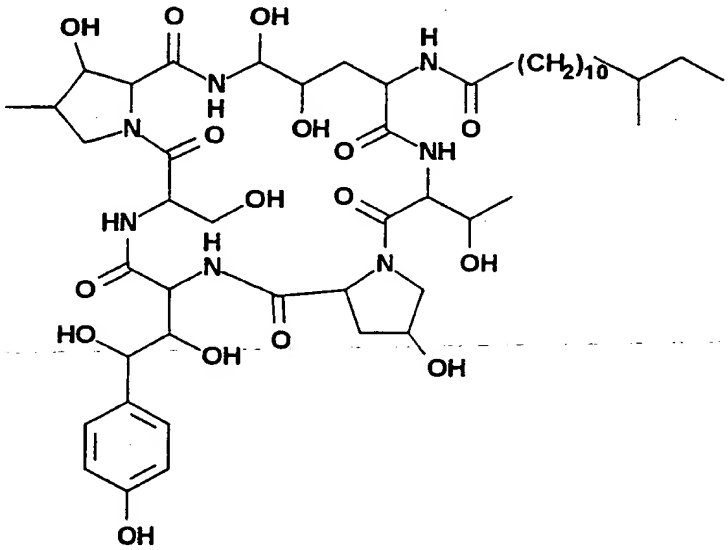
wherein W, X, Y, Z, R and R' are as defined herein below :

		W	X	Y	Z	R	R'
1.	Echinocandin B	OH	OH	OH	OH	CH_3	Linoleoyl
2.	Pneumocandin A_0	OH	OH	OH	OH	CH_2-$CONH_2$	10,12-Dimethyl-myristoyl
3.	Pneumocandin A_1	H	OH	OH	OH	CH_2-$CONH_2$	"
4.	Pneumocandin A_2	OH	OH	H	H	CH_2-$CONH_2$	"
5.	Pneumocandin B_0	OH	OH	OH	OH	CH_2-$CONH_2$	"
6.	Pneumocandin B_2	OH	OH	H	H	CH_2-$CONH_2$	"
7.	Pneumocandin C_0	OH	OH	OH	OH	CH_2-$CONH_2$	"
8.	Mulundocandin	OH	OH	OH	OH	H	12-Methyl-tetradecanoyl

to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below:

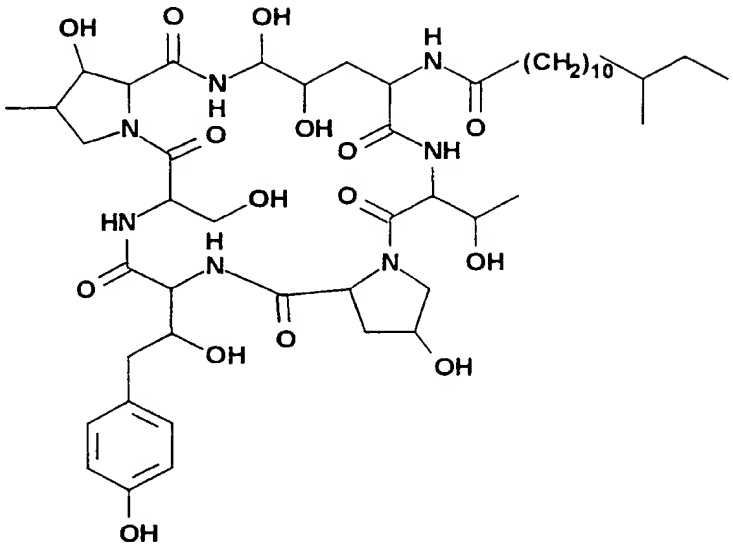
		W	X	Y	Z	R	R'
1.	Deoxyechinocandin B (Echinocandin C)	OH	H	OH	OH	CH_3	Linoleoyl
2.	Deoxypneumocandin A_0	OH	H	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3.	Deoxypneumocandin A_1	H	H	OH	OH	CH_2-$CONH_2$	"
4.	Deoxypneumocandin A_2	OH	H	H	H	CH_2-$CONH_2$	"
5.	Deoxypneumocandin B_0	OH	H	OH	OH	CH_2-$CONH_2$	"
6.	Deoxypneumocandin B_2	OH	H	H	H	CH_2-$CONH_2$	"
7.	Deoxypneumocandin C_0	OH	H	OH	OH	CH_2-$CONH_2$	"
8.	Deoxymulundocandin	OH	H	OH	OH	H	12-Methyl tetra-decanoyl,

particularly to a process for the conversion of mulundocandin (compound of the formula II)



(II)

to deoxymulundocandin (compound of the formula III)



(III)

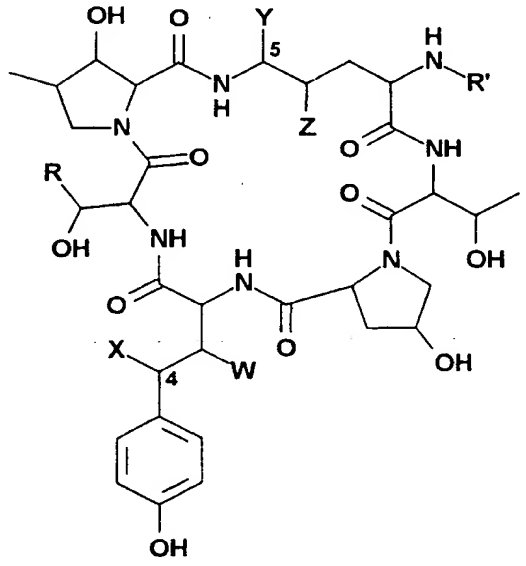
1,3-β-glucan synthesis inhibitors are effective antifungal agents against Candida albicans and also Pneumocystis carini, an opportunistic organism responsible for an often fatal pneumonitis among HIV patients and other immunocompromised hosts. Of all the structural classes of 1,3-β- glucan synthesis inhibitors, only the echinocandins received considerable attention [Ref : J. Med. Chem. 35, 198-200 (1992)]. Echinocandin class of peptides are cyclic hexapeptides having a lipophilic side chain.

Several methods for the conversion of echinocandins to the corresponding deoxy analogues under acidic conditions have been reported [Ref : Tetrahedron Letts., 33, 4529-4532 (1992); US Patent Appl. No. 222157 dated April 4, 1994]. The above methods involve selective reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues with prior protection / deprotection of the equally facile C5-Orn (ornithine) hydroxyl group.

Mulundocandin [J.Antibiotics, 40, 275-280 and 281-289 (1987)] and deoxymulundocandin [Indian patent No. IN 169830 ; J.Antibiotics, 45, 618-623 (1992)] having antifungal properties were isolated from Aspergillus sydowii (Bainier and Sartory) Thom and Church var. Nov. Mulundensis Roy (culture no.HIL Y-30462). Deoxymulundocandin was found to possess better antifungal activity than mulundocandin. However, the production of deoxymulundocandin during the fermentation was 200 times less than that of mulundocandin.

We have found out by extensive research and experimentation that echinocandin class of peptides of the formula I may be converted to the corresponding C4-htyr monodeoxy analogues, particularly mulundocandin to deoxymulundocandin under neutral conditions. Accordingly, the object of the present invention is to provide a process for the conversion of echinocandin class of peptides of the formula I to the corresponding C4-homotyrosin monodeoxy analogues, particularly mulundocandin (compound of formula II) to deoxymulundocandin (compound of formula III).

According to the invention, there is provided a process for the conversion of echinocandin class of peptides of the formula I



(I)

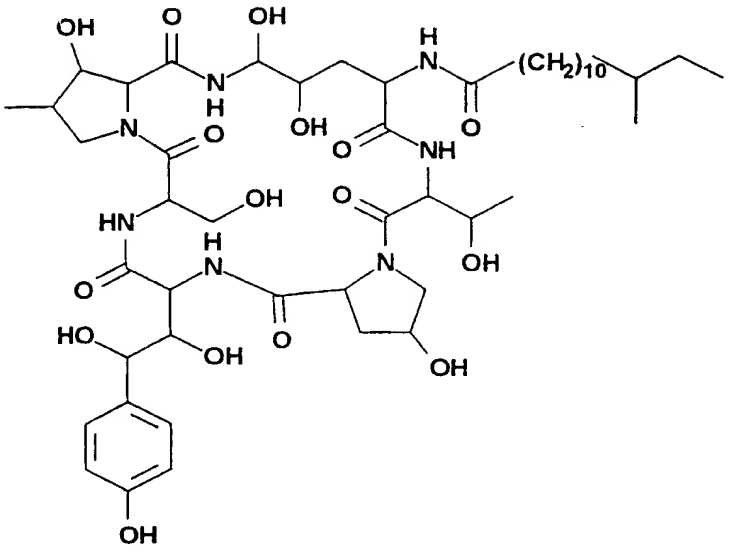
wherein W, X, Y, Z, R and R' are as defined herein below :

		W	X	Y	Z	R	R'
1. Echinocandin B		OH	OH	OH	OH	CH_3	Linoleoyl
2. Pneumocandin A_0		OH	OH	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3. Pneumocandin A_1		H	OH	OH	OH	CH_2-CO-NH_2	"
4. Pneumocandin A_2		OH	OH	H	H	CH_2-CO-NH_2	"
5. Pneumocandin B_0		OH	OH	OH	OH	CH_2-CO-NH_2	"
6. Pneumocandin B_2		OH	OH	H	H	CH_2-CO-NH_2	"
7. Pneumocandin C_0		OH	OH	OH	OH	CH_2-CO-NH_2	"
8. Mulundocandin		OH	OH	OH	OH	H	12-Methyl-tetradecanoyl

to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below:

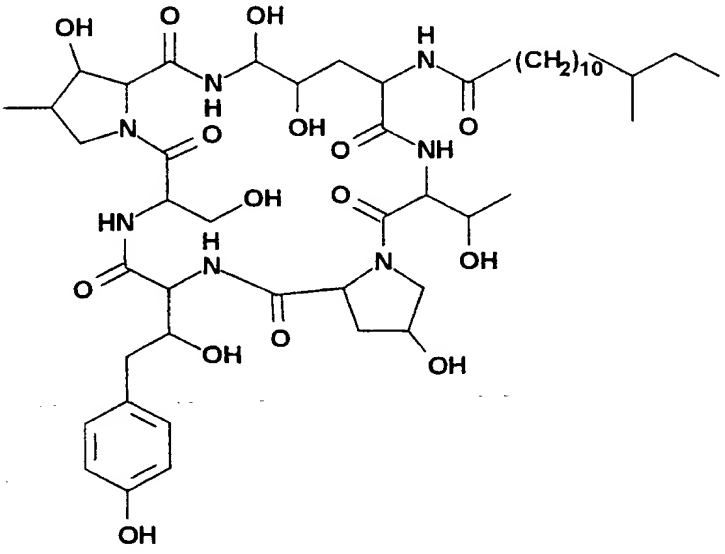
		W	X	Y	Z	R	R'
1. Deoxyechinocandin B (Echinocandin C)		OH	H	OH	OH	CH_3	Linoleoyl
2. Deoxypneumocandin A_0		OH	H	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3. Deoxypneumocandin A_1		H	H	OH	OH	CH_2-CO-NH_2	"
4. Deoxypneumocandin A_2		OH	H	H	H	CH_2-CO-NH_2	"
5. Deoxypneumocandin B_0		OH	H	OH	OH	CH_2-CO-NH_2	"
6. Deoxypneumocandin B_2		OH	H	H	H	CH_2-CO-NH_2	"
7. Deoxypneumocandin C_0		OH	H	OH	OH	CH_2-CO-NH_2	"
8. Deoxymulundocandin		OH	H	OH	OH	H	12-Methyl tetra-decanoyl

particularly to a process for the conversion of mulundocandin (compound of the formula II



(II)

to deoxymulundocandin (compound of the formula III)



which consists of a single step selective reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues particularly under neutral conditions without prior protection / deprotection of the equally facile C5-Orn (ornithine) hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture.

The conversion of echinocandins to their monodeoxy analogues by selective reduction at C4-htyr may be effected by hydrogenolysis with Raney nickel in solvents such as methanol, ethanol, or dioxane at pH 3-9. Preferably, the selective reduction is carried out by hydrogenolysis with Raney nickel in ethanol at pH 7 and room temperature in the ratio of 6.8 ml Raney nickel per millimole of mulundocandin.

The monodeoxy compounds of the invention may, for example, be purified from the crude reaction mixture as follows :

By fractionation using normal phase chromatography (using alumina or silica gel as stationary phase and eluents such as petroleum ether, ethyl acetate, dichloromethane, chloroform, methanol or combinations thereof), reverse phase chromatography (using reverse phase silica gel like dimethyloctadecylsilylsilica gel, also called RP-18 or dimethyloctylsilylsilica gel also called RP-8 as stationary phase and eluents such as water, buffers such as phosphate, acetate, citrate (pH 2-8) and organic solvents such as methanol, acetonitrile, acetone, tetrahydrofuran or combination of the solvents), gel permeation chromatography - using resins such as "Sephadex LH-20®" (Pharmacia Chemical Industries, Sweden), TSKgel Toyopearl HW (TosoHaas, Tosoh Corporation, Japan) in solvents such as methanol, chloroform or ethyl acetate or their combination or Sephadex G-10 and G-25 in water; or by counter-current chromatography using a biphasic eluent system made up of two or more solvents such as water, methanol, ethanol, *iso*-propanol, *n*-propanol, tetrahydrofuran, acetone, acetonitrile, methylene chloride, chloroform, ethylacetate, petroleum ether, benzene and toluene. These techniques may be used repeatedly or a combination of the different techniques may be used. Counter-

current chromatography (liquid-liquid chromatography) using a biphasic eluent system on ITO coil is preferred for purification of the compounds of the invention.

The following experimental example is illustrative of the present invention but not limitative of the scope thereof.

Example 1

Mulundocandin (220 mg, 2.2 mM) in ethanol (8 ml)) was stirred with 15 ml of W-2 Raney nickel (pH 7) in ethanol (30 ml) for 3 hours at room temperature. After standing for 15 minutes the supernatent solution was decanted and Raney nickel washed with 3 x 30 ml. ethanol with stirring and filtered. Combined ethanolic solutions were concentrated by distillation under a reduced pressure of 60-70 mm/Hg at 35° C to obtain 160 mg (75%) of crude deoxymulundocandin as a slightly green solid.

The crude product was purified by liquid-liquid chromatography on ITO coil using upper layer of CH_2Cl_2 : MeOH : *n*-PrOH :H_20 as the stationary phase and the lower layer as the mobile phase in an ascending mode. The coils (15 + 25 + 215 ml) were connected in series and a flow rate of 0.6 ml/min. at a piston stroke of 60 and pressure 0.5 bars was maintained. The purification of deoxymulundocandin was monitored both by bioactivity against *Candida albicans* and *Aspergillus niger* and by analytical High Pressure Liquid Chromatography (HPLC) [column : (10 x 0.4 cm + 3 x 0.4 cm) ODS-Hypersil, 10μ; mobile phase: 50:50 CH_3CN : H_20 ; flow rate : 1 ml/min; Wavelength : 220 nm.) The fractions (4.5 ml each) containing deoxymulundocandin were combined, concentrated by distillation under a reduced presssure of 60-70 mm/Hg at 35°C and lyophilized to yield pure deoxymulundocandin [65 mg (30% yield)]. Also recovered during the above purification of deoxymulundocandin was unreacted mulundocandin in 10% yield.

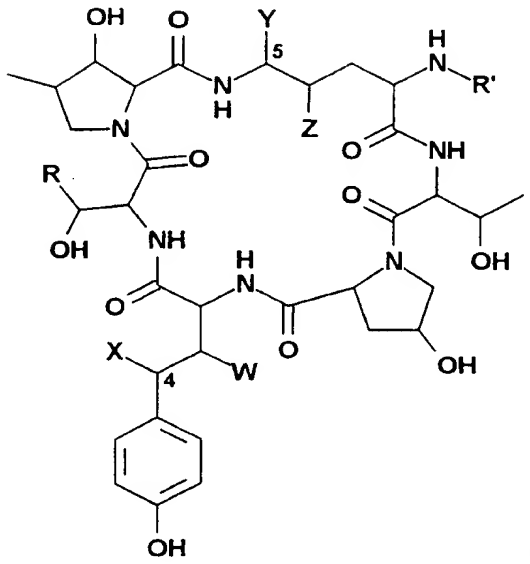
The semi-synthetic deoxymulundocandin was identical in all respects to the naturally isolated compound and the physico-chemical data is given in Table 1.

TABLE 1

Appearance :	White powder
Melting point:	170-172°C
$[\alpha]_D$:	- 36.6° (*c* 0.25, MeOH)
HPLC RT :	4.42 min
FAB-MS (Fast Atom: Bombardment mass)	1014.7 $(M + Na)^+$
^1H NMR (300 MHz,: CD_3OD)	Figure 1 of the accompanying drawings
^{13}C NMR (75 MHz, : CD_3OD)	Figure 2 of the accompanying drawings

Claims:

1. A process for the conversion of echinocandin class of peptides of the formula I



(I)

wherein W, X, Y, Z, R and R' are as defined herein below :

		W	X	Y	Z	R	R'
1.	Echinocandin B	OH	OH	OH	OH	CH_3	Linoleoyl
2.	Pneumocandin A_0	OH	OH	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3.	Pneumocandin A_1	H	OH	OH	OH	CH_2-CO-NH_2	"
4.	Pneumocandin A_2	OH	OH	H	H	CH_2-CO-NH_2	"
5.	Pneumocandin B_0	OH	OH	OH	OH	CH_2-CO-NH_2	"
6.	Pneumocandin B_2	OH	OH	H	H	CH_2-CO-NH_2	"
7.	Pneumocandin C_0	OH	OH	OH	OH	CH_2-CO-NH_2	"
8.	Mulundocandin	OH	OH	OH	OH	H	12-Methyl-tetradecanoyl

to their C4-homotyrosine monodeoxy analogues of the formula I, wherein W, X, Y, Z, R and R' are as defined herein below

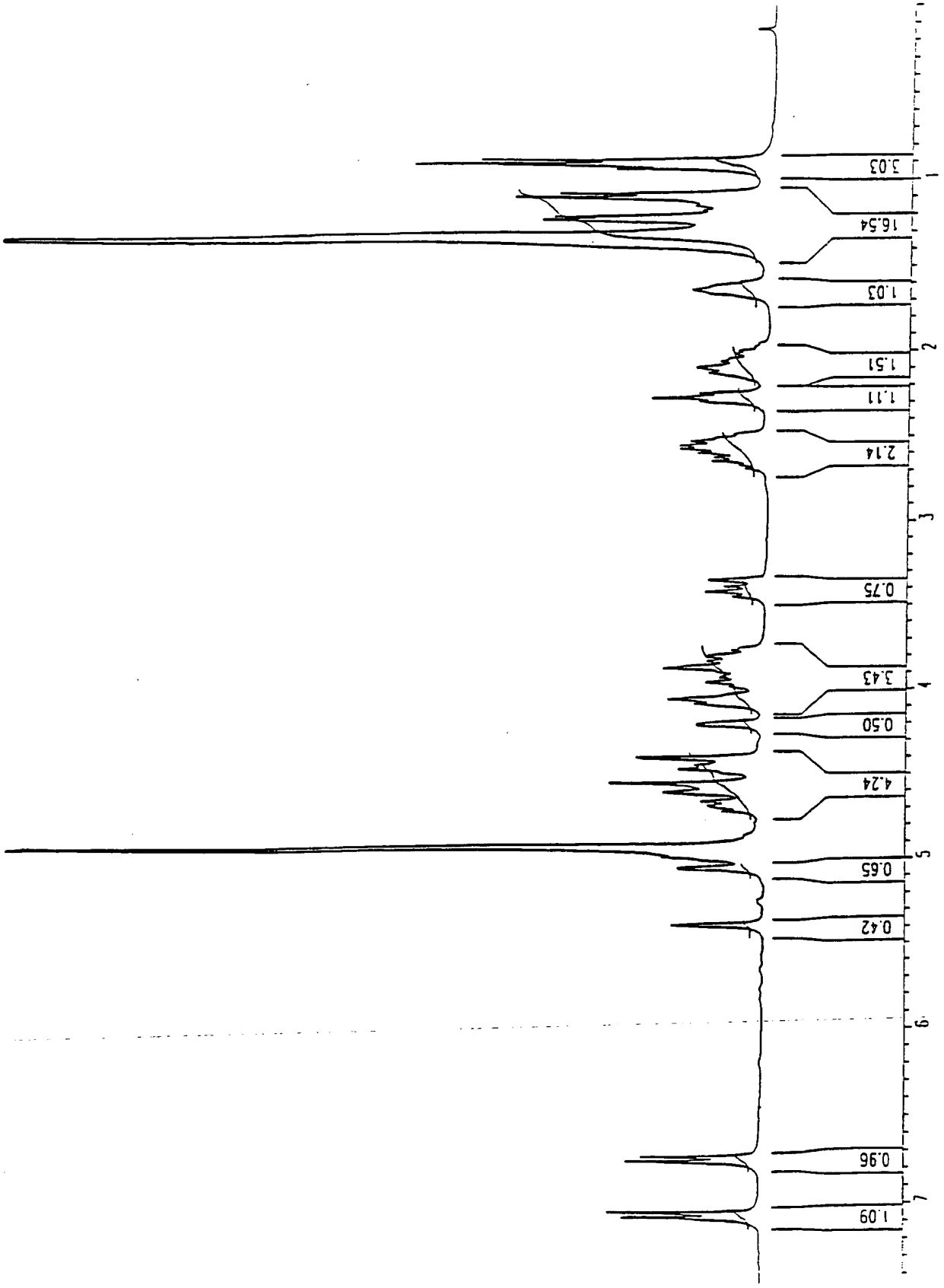
		W	X	Y	Z	R	R'
1.	Deoxyechinocandin B (Echinocandin C)	OH	H	OH	OH	CH_3	Linoleoyl
2.	Deoxypneumocandin A_0	OH	H	OH	OH	CH_2-CO-NH_2	10,12-Dimethyl-myristoyl
3.	Deoxypneumocandin A_1	H	H	OH	OH	CH_2-$CONH_2$	"
4.	Deoxypneumocandin A_2	OH	H	H	H	CH_2-$CONH_2$	"
5.	Deoxypneumocandin B_0	OH	H	OH	OH	CH_2-$CONH_2$	"
6.	Deoxypneumocandin B_2	OH	H	H	H	CH_2-$CONH_2$	"
7.	Deoxypneumocandin C_0	OH	H	OH	OH	CH_2-$CONH_2$	"
8.	Deoxymulundocandin	OH	H	OH	OH	H	12-Methyl tetra-decanoyl

which consists of a single step selective reduction of C4-htyr (homotyrosine) hydroxyl group of echinocandins to their monodeoxy analogues under neutral conditions without prior protection / deprotection of the equally facile C5-Orn (ornithine) hydroxyl group and purification of the monodeoxy compound from the crude reaction mixture.

2. A process as claimed in claim 1, wherein Mulundocandin is converted to Deoxymulundocandin.

3. A process as claimed in claims 1 or 2, wherein the reduction reaction is carried out by hydrogenolysis with Raney nickel in ethanol at pH 7 and room temperature.

4. A process as claimed in claims 1 to 3, wherein the hydrogenolysis is carried out in the ratio of 6.8 ml of Raney nickel per millimole of mulundocandin.


3.03
16.54
1.03
1.51
1.11
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0.75
3.43
0.50
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2
3
4
5
6
7
(ppm)

Fig. 1

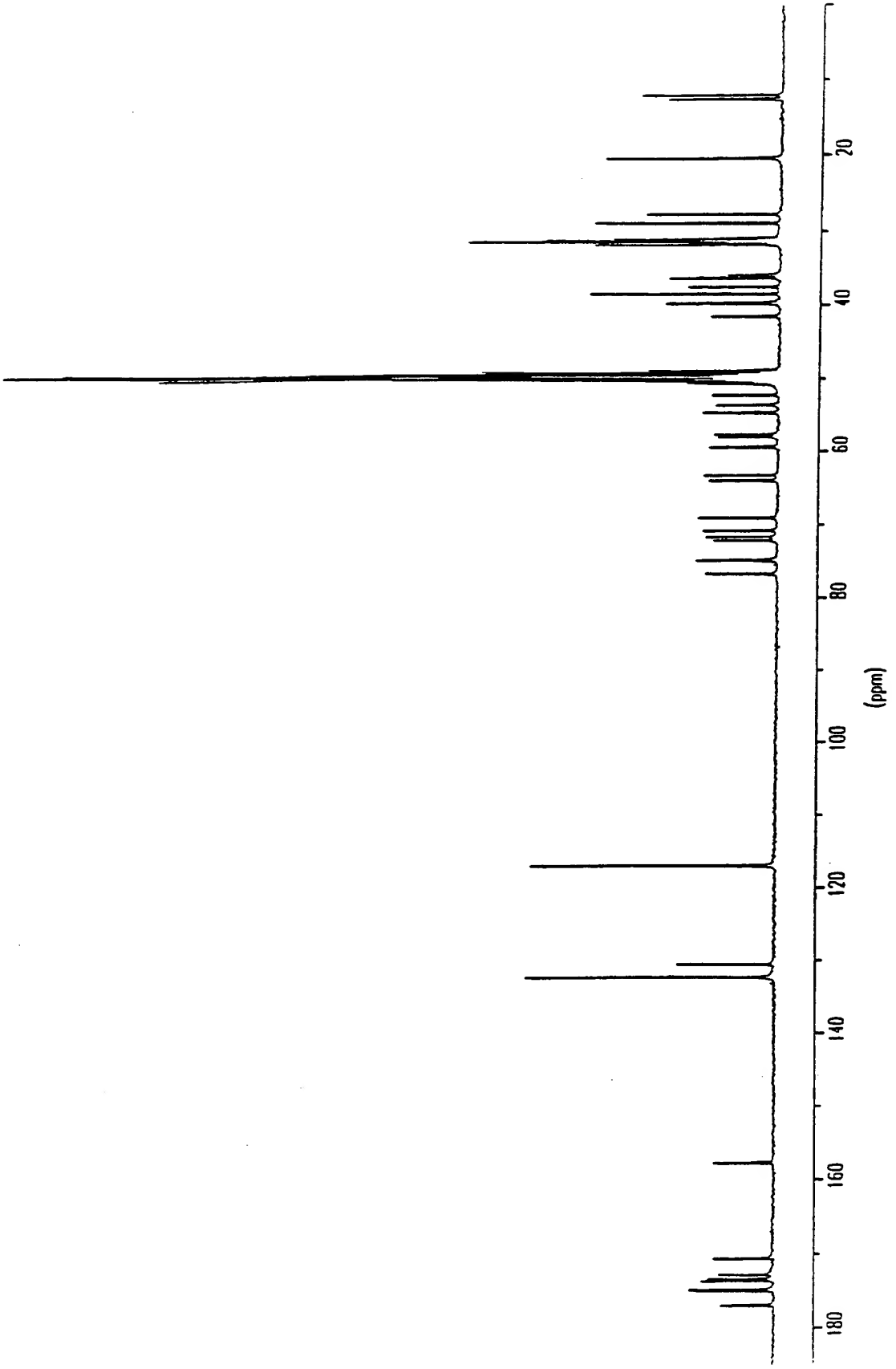

Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/02715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K7/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 535 959 A (MERCK & CO INC) 7 April 1993 (1993-04-07) example XVIII ---	1-4
A	EP 0 535 968 A (MERCK & CO INC) 7 April 1993 (1993-04-07) example VII ---	1-4
A	BALKOVEC J M ET AL: "REDUCTION STUDIES OF ANTIFUNGAL ECHINOCANDIN LIPOPEPTIDES ONE STEP CONVERSION OF ECHINOCANDIN B TO ECHINOCANDIN C" TETRAHEDRON LETTERS, vol. 33, no. 32, 4 August 1992 (1992-08-04), pages 4529-4532, XP000571502 cited in the application the whole document --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 1999	20/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 644 199 A (FUJISAWA PHARMACEUTICAL CO) 22 March 1995 (1995-03-22) See especially page 11, line 50 to page 12, line 16	1-4
A	WO 96 08266 A (MERCK & CO INC ;BALKOVEC JAMES M (US); BOUFFARD FRANCES A (US); HA) 21 March 1996 (1996-03-21) See page 19, lines 28-35; page 24, lines 5-16	1-4
A	EP 0 459 564 A (MERCK & CO INC) 4 December 1991 (1991-12-04) the whole document	1-4

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PC./EP 99/02715

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0535959 A	07-04-1993	AT 147757 T	15-02-1997
		CA 2079171 A	02-04-1993
		DE 69216746 D	27-02-1997
		DE 69216746 T	03-07-1997
		DK 535959 T	09-06-1997
		ES 2098455 T	01-05-1997
		GR 3022292 T	30-04-1997
		JP 2096302 C	02-10-1996
		JP 6234795 A	23-08-1994
		JP 7121958 B	25-12-1995
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		CA 2079172 A	02-04-1993
		JP 2075135 C	25-07-1996
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EP 0644199 A	22-03-1995	AU 681119 B	21-08-1997
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		CA 2123921 A	18-11-1994
		CN 1100104 A	15-03-1995
		HU 68385 A	28-06-1995
		JP 6340693 A	13-12-1994
		US 5569646 A	29-10-1996
		US 5693750 A	02-12-1997
		ZA 9403356 A	28-03-1995
WO 9608266 A	21-03-1996	AU 692308 B	04-06-1998
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		JP 10505836 T	09-06-1998
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		CA 2043378 A	30-11-1991
		JP 4235196 A	24-08-1992

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
1998/L020 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/02715	22/04/1999	23/04/1998
International Patent Classification (IPC) or national classification and IPC C07K7/56		
Applicant AVENTIS PHARMA DEUTSCHLAND GMBH		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
16/11/1999	24.05.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer G. Willière Telephone No. +49 89 2399 8548

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/02715

I. Basis of th r port

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-9 as originally filed

Claims, No.:

1-4 as originally filed

Drawings, sheets:

1/2-2/2 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they hav b en considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-4
	No:	Claims
Inventive step (IS)	Yes:	Claims 1-4
	No:	Claims
Industrial applicability (IA)	Yes:	Claims 1-4
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: EP-A-0 535 959 (MERCK & CO INC) 7 April 1993 (1993-04-07)
   D2: EP-A-0 535 968 (MERCK & CO INC) 7 April 1993 (1993-04-07)
   D3: BALKOVEC J M ET AL: 'REDUCTION STUDIES OF ANTIFUNGAL ECHINOCANDIN LIPOPEPTIDES ONE STEP CONVERSION OF ECHINOCANDIN B TO ECHINOCANDIN C' TETRAHEDRON LETTERS, vol. 33, no. 32, 4 August 1992 (1992-08-04), pages 4529-4532, **cited in the application**
   D4: EP-A-0 644 199 (FUJISAWA PHARMACEUTICAL CO) 22 March 1995 (1995-03-22)
   D5: WO 96 08266 A (MERCK & CO INC ;BALKOVEC JAMES M (US); BOUFFARD FRANCES A (US); HA) 21 March 1996 (1996-03-21)
   D6: EP-A-0 459 564 (MERCK & CO INC) 4 December 1991 (1991-12-04)

2. The present application relates to a process which consist in a single step reduction of the C-4 hydroxyl group of inter alia echinocandins to their monodeoxy analogues under **neutral** conditions without prior protection/deprotection.

3. Example XVIII of D1, example VII of D2, D3, process 1 of D4 (see pages 11 and 12) and D6 disclose a process for a selective single step reduction of the C-4 hydroxyl group of compounds as described in the present application to their monodeoxy analogues under **acidic** conditions.

4. D5 relates to the preparation of aza cyclohexapeptide compounds wherein a nitrile moity is reduced in an intermediate step to an amine (see R_1 of seq.id. no. 1) without specifying the reduction of the C-4 hydroxyl group to the monodeoxy analogue.

5. It thus appears that the presently claimed subject-matter is both novel and cannot

be obviously derived from what is known from D1 to D6 (Article 33(2) and (3) PCT). The Applicant should however consider the objection made under item VIII below.

Re Item VIII

Certain observations on the international application

1. Claims 1 and 2 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claims attempt to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. **The technical features necessary for achieving this result should be added.**

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
1998/L020 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 02715	22/04/1999	23/04/1998
Applicant		
HOECHST MARION ROUSSEL DEUTSCHLAND GMBH et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
CT/EP 99/02715

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K7/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 535 959 A (MERCK & CO INC) 7 April 1993 (1993-04-07) example XVIII ---	1-4
A	EP 0 535 968 A (MERCK & CO INC) 7 April 1993 (1993-04-07) example VII ---	1-4
A	BALKOVEC J M ET AL: "REDUCTION STUDIES OF ANTIFUNGAL ECHINOCANDIN LIPOPEPTIDES ONE STEP CONVERSION OF ECHINOCANDIN B TO ECHINOCANDIN C" TETRAHEDRON LETTERS, vol. 33, no. 32, 4 August 1992 (1992-08-04), pages 4529-4532, XP000571502 cited in the application the whole document --- -/--	1-4

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
10 September 1999	20/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted] ernational Application No
PCT/EP 99/02715

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 644 199 A (FUJISAWA PHARMACEUTICAL CO) 22 March 1995 (1995-03-22) See especially page 11, line 50 to page 12, line 16	1-4
A	WO 96 08266 A (MERCK & CO INC ;BALKOVEC JAMES M (US); BOUFFARD FRANCES A (US); HA) 21 March 1996 (1996-03-21) See page 19, lines 28-35; page 24, lines 5-16	1-4
A	EP 0 459 564 A (MERCK & CO INC) 4 December 1991 (1991-12-04) the whole document	1-4

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]mation on patent family members

[redacted]ernational Application No
PCT/EP 99/02715

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0535959 A	07-04-1993	AT 147757 T	15-02-1997
		CA 2079171 A	02-04-1993
		DE 69216746 D	27-02-1997
		DE 69216746 T	03-07-1997
		DK 535959 T	09-06-1997
		ES 2098455 T	01-05-1997
		GR 3022292 T	30-04-1997
		JP 2096302 C	02-10-1996
		JP 6234795 A	23-08-1994
		JP 7121958 B	25-12-1995
EP 0535968 A	07-04-1993	US 5348940 A	20-09-1994
		CA 2079172 A	02-04-1993
		JP 2075135 C	25-07-1996
		JP 6234794 A	23-08-1994
		JP 7100715 B	01-11-1994
EP 0644199 A	22-03-1995	AU 681119 B	21-08-1997
		AU 6199494 A	24-11-1994
		CA 2123921 A	18-11-1994
		CN 1100104 A	15-03-1995
		HU 68385 A	28-06-1995
		JP 6340693 A	13-12-1994
		US 5569646 A	29-10-1996
		US 5693750 A	02-12-1997
		ZA 9403356 A	28-03-1995
WO 9608266 A	21-03-1996	AU 692308 B	04-06-1998
		AU 3630395 A	29-03-1996
		CA 2197209 A	21-03-1996
		EP 0781141 A	02-07-1997
		JP 10505836 T	09-06-1998
		US 5668105 A	16-09-1997
EP 0459564 A	04-12-1991	US 5159059 A	27-10-1992
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